Prevalence and etiology of strabismus in Down syndrome: A systematic review and meta-analysis with a focus on ethnic differences in the esotropia/exotropia ratio

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Running Title: Strabismus in Down Syndrome

Review Article: 4,000 word maximum, 5 Figures, 1 Table

Word count: 3,947

Abstract

Purpose. We sought to determine the prevalence of strabismus and the esotropia/exotropia ratio in Down syndrome. Wide ranges of an increased strabismus prevalence have been reported and it is unclear by how much esotropia exceeds exotropia in people with Down syndrome.

Methods. We compiled in a systematic review and meta-analysis the results of over 100 studies that report the strabismus prevalence and ratio of esotropia/exotropia in cohorts of Down syndrome. We calculated the pooled global prevalence and established the geographical distribution of the strabismus prevalence and the esotropia/exotropia ratio.

Results. The ethnically-adjusted global prevalence of strabismus in Down syndrome is 30.2%. In subjects 15 years and older, the global prevalence is 53.2%, and the lifetime prevalence is 51.0%. In populations which normally have more esotropia than exotropia (e.g., Caucasians), Down syndrome subjects have a further increased bias towards esotropia. In populations which normally have more exotropia (e.g., West Africans, Asians and Hispanics), Down syndrome subjects have a significantly lower esotropia/exotropia ratio (3.21) than reported in Caucasians with Down syndrome (9.98).

Conclusion. Worldwide, about 1.81 million people with Down syndrome have strabismus: 1.42 million of them have esotropia, and 0.37 million have exotropia. Differences in the esotropia/exotropia ratio between ethnicities point to the orbital anatomy as a major contributing factor to the etiology of strabismus in Down syndrome.

The narrow-set eyes (reduced orbital width) in Down syndrome favor esotropia over exotropia, especially in Caucasians, thus explaining why Down syndrome patients from different ethnicities have different prevalences of esotropia and exotropia.

249/250 words

Key words: strabismus, Down syndrome, trisomy 21, esotropia, exotropia, global, ethnicity, geographic mapping, etiology

Funding Details: This work was supported by the National Institutes of Health under Grant EY031729 to CSvB; National Institutes of Health under Grant GM103554 to CSvB; and Office of Medical Research, University of Nevada, Reno, School of Medicine under a microgrant (AC).

Disclosure Statement: The authors declare no competing interests.

Introduction

Since the discovery of an increased frequency of strabismus in people with Down syndrome,[1-4] many authors have reported the prevalence of strabismus in selected cohorts. Review articles and primary research articles have reported diverse ranges of the strabismus prevalence, from 1.9% to 100% (Supplemental Table 1). Arbitrary selections of the considered studies led to the variety of the reported ranges in review articles, and the true prevalence of strabismus in Down syndrome has remained elusive. In addition, reports of the ratio of esotropia to exotropia in Down syndrome have been widely divergent. Nearly half of the European studies in the 20th century reported exclusively esotropia, and no exotropia in their cohorts, while most of the studies from Asia and Africa reported at least 25% of the strabismus cases to be exotropia. Some of the differences may be due to Eurocentric bias and common neglect of studies published in non-English languages. Our review includes studies published in thirteen languages other than English and is the first review that systematically compiles relevant studies. The previous most thorough reviews considered only a small fraction (13 to 31) [5-9] of the 142 available reports on the prevalence of strabismus in Down syndrome.

Several authors reported that the strabismus in Down syndrome children develops at a significantly later age than in the normal population.[4-5,10-20] Probably because of the late onset of the acquired strabismus in Down syndrome, a remarkably low percentage of amblyopia was noted in many studies.[5,15,21-31] Some authors reported

ethnic differences in the frequency of esotropia vs exotropia in Down syndrome,[14,17,32-39] but possible underlying mechanisms were not explored.

The etiology of strabismus in Down syndrome has remained enigmatic and controversial. Several potential causes of strabismus in Down syndrome were discussed, including the narrow orbital width in Down syndrome, opacity of the lens, muscle hypotonia, refractive errors with lack of normally occurring emmetropization, accommodation weakness, retinal abnormalities, visual cortex abnormalities, and various combinations of the above conditions.[5,17-19,21,37,40-51] The etiology of strabismus in Down syndrome differs substantially from that in the normal population.[49-51] Yet, a comprehensive review of the etiology of strabismus in Down syndrome is lacking.

In our systematic review and meta-analysis,[52] we provide information about the true global prevalence of strabismus in people with Down syndrome. We estimate global numbers of esotropia and exotropia cases that take into account the Eurocentric bias due to the large majority of studies examining Caucasians of European ancestry. We provide a geographic world map of the esotropia/exotropia ratio in Down syndrome, and we review and synthesize opinions and arguments about the etiology of strabismus in Down syndrome.

Materials and Methods

Search Strategy

For our systematic review of the literature, we adhered to the PRISMA guidelines.[53] Reports of studies were identified through a search of two databases: Google Scholar and PubMed, with unrestricted years. We used the keywords “Down syndrome”, “trisomy 21”, “strabismus”, “esotropia”, and “exotropia” in Google Scholar, and “Down syndrome” or “trisomy 21” and “strabismus”, as well as “Down syndrome” or “trisomy” and “squint” in PubMed. Only English terms were used for the search strategy, but we retrieved 29 studies that were published in languages other than English, because they had an English title and/or abstract, or were cited in relevant studies. Studies published in languages besides English included German (5 studies), Turkish (5), French (3), Portuguese (3), Spanish (3), Norwegian (2), Polish (2), Chinese (1), Czech (1), Italian (1), Japanese (1), Russian (1), and Swedish (1). All references cited in eligible articles were examined to identify additional relevant studies. Titles were screened, and when potentially relevant, the abstract was evaluated to decide whether full-text should be obtained to verify eligibility (Fig. 1). We failed to obtain an abstract or full-text in 3 of 817 sources.

Inclusion/Exclusion Criteria

To be eligible for inclusion in our systematic review, studies had to report the numerical prevalence of strabismus in humans with Down syndrome (non-human primates were

not considered)[54] and/or provide the ratio of esotropia vs exotropia in a Down syndrome cohort. We excluded reviews only, case reports, and abstracts at meetings when later published as a peer-reviewed paper. Sorted by geography, we included 55 studies on Caucasians in Europe,[1-5,11,28,33-34,40,44,47-49,55-94] 29 studies from North America or Australia,[21,23,29,31,42,95-118] 18 from the Middle East,[8-9,12-13,26-27,45,119-129] 8 from Latin America,[10,25,30,130-134] 13 from East Asia,[14,32,35,135-144] 12 from South Asia,[17-18,20,145-153] and 7 from Africa or on Africans,[154-160] for a total of 142 eligible studies (Supplemental Table 1). For the final analyses, we excluded 5 studies that reported on duplicate cohorts.

Data Extraction and Analyses

Data were extracted by using pre-designed tables, including year of publication, first author name, country, geographic region, age range, cohort size, number of cases of strabismus, and the type of strabismus: horizontal vs. vertical, and among the horizontal strabismus, how many cases of esotropia, how many cases of exotropia and the esotropia/exotropia ratio. Cases of microtropia and paralytic strabismus were not included. When gender distribution in the cohort was reported, we compiled such information, and also when information on gender in strabismus cases was provided. The percentage of strabismus cases was calculated from the number of cases actually examined per cohort. We conducted subgroup analyses between continents and ethnicities. Because of ethnic differences between populations in the ratio of esotropia/exotropia, the prevalence for Caucasians and non-Caucasians was estimated

separately and weighted by population size to generate a global estimate of the esotropia/exotropia ratio and numbers of esotropia and exotropia cases in people with Down syndrome. This was also necessary to prevent bias: a large majority of available studies examined people of European ancestry. We had sufficient data for Caucasians and populations from the Middle East to assess generational (longitudinal) trends. We also performed subgroup analyses for different age ranges and estimated the lifetime prevalence of strabismus in Down syndrome.

Statistical Analyses

A major purpose of our meta-analysis was to generate a more precise and reliable estimate of the prevalence of strabismus among people with Down syndrome and to infer the global number of Down syndrome cases with strabismus. A second purpose was to analyze the esotropia/exotropia (ET/XT) ratio to determine potential differences between ethnicities. For this analysis, three of the studies were grouped by ethnicity rather than geography because the ethnicity of the subjects differed from the geography (Supplementary Table 1).[10,116,159] Pooled analyses were performed for strabismus prevalence in Down syndrome and the ET/XT ratio. The heterogeneity among studies was evaluated by Cochran's Q test and the I^2 index.[161-162] The random-effect models were used to conservatively diminish the heterogeneity between studies.[162] The study weights were obtained based on the DerSimonian-Laird method.[162] Subgroup pooled analyses were conducted by region/ethnicity, separately for prevalence and for the ET/XT ratio, to assess differences between Caucasians and non-Caucasians. When

calculating the ET/XT ratio, a continuity correction of 0.5 was applied to studies with zero XT cases by adding 0.5 to both ET and XT cases to avoid division by zero.[163] Meta-regression analyses were performed to test associations between independent variables (age, gender, ethnicity, year of publication) and response variables (prevalence, ET/XT ratio). The risk of publication bias was evaluated using funnel plots and Egger's test (Supplemental Figs. 1, 3).[164] The significance level was set to 0.05. All meta-analyses were performed using the Stata SE 16.0 software (StataCorp, TX, USA).

Results

We included in our analyses 137 of the total 142 eligible studies (after removal of 5 duplicate publications of largely the same cohort). Their geographical distribution and cohort sizes are depicted in Figure 2A. Cohort sizes varied from 3 to 1,539, with a mean cohort size of 122.5 and a total number of 16,781 subjects in the cohorts. There was no publication bias for Caucasians, but there was bias for Non-Caucasians based on funnel plots (Supplemental Fig. 1A,B). 60.6% of all eligible studies (83/137) and 65.3% of all subjects in the cohorts were on Caucasians or mostly Caucasians, while Asians and Africans were underrepresented: only 16.1% of all subjects, combined, were Asians and Africans. The world map indicates that Caucasians have a larger strabismus prevalence than other ethnicities (Fig. 2A). We therefore tested in a subgroup analysis whether there was a significant difference in prevalence between Caucasians and other ethnicities or geographical areas. Caucasians have a 39.0% prevalence, while Non-Caucasians have a 28.7% prevalence – a significant difference (p=0.001). The Forest plot for the prevalence of strabismus in Down syndrome in Caucasians and Non-Caucasians is shown in Fig. 3A,B. When adjusted for population size of ethnicities (1.2 billion Caucasians, 0.5 billion in the Middle East, 1.9 billion South Asians, 2.4 billion East Asians, 1.3 billion Africans and 0.7 billion Hispanics), the global prevalence of strabismus in Down syndrome was 30.2% (95% confidence interval, CI, = 29.2-31.3%). The ethnically-adjusted pooled prevalence of strabismus in Down syndrome allows us to estimate the total number of people with Down syndrome – worldwide – who have strabismus. Based on estimates of 6 million people worldwide with Down syndrome,[165]

we conclude that 1.81 million of them have strabismus, with 1.42 million having esotropia and 0.37 million having exotropia (see below).

AGE. Studies examined strabismus prevalence for different age groups of Down syndrome. The prevalence was low in the first three years and increased at about 4 years of age.[4,9-17,19-20] The prevalence of strabismus in cohorts of subjects below 3 years of age (n=4 studies, n=603 subjects) was 15.6% (CI = 2.6-35.6%, Fig. 3C). We estimated the lifetime prevalence of strabismus in Down syndrome using data from cohorts with subjects 15 years of age and older (n=11 studies, n=2,381 subjects). In these older subjects, the prevalence of strabismus was 53.2% (CI = 42.1-64.1%) (Fig. 3D, 4A). Studies on adults only (n=8 studies; n=2,045 subjects) showed a 51.0% (CI = 38.0-63.8%) prevalence of strabismus. Based on the strabismus prevalence and lifetime prevalence, we estimate that the current global number of Down syndrome people with strabismus is 1.81 million, but that 3.19 million will develop strabismus during their lifetime.

GENDER. Among the 137 studies, 78 reported the gender distribution in the cohort (total number of subjects in those cohorts=11,036): the average sex ratio in the time period from 1910 to 2024 was 1.21 males per female, which is nearly identical to a previous review (1.22 in the 1990s).[166] Only 7 studies (cohort size = 793)[1,4,9,27,71-72,96] reported the gender distribution also among strabismus cases. The pooled prevalence of strabismus in males was 36.2% (CI = 22.3-51.2%) and in females 38.6% (CI = 25.7-52.2%), which is no significant difference (p=0.866, Fig. 4B).

TYPES OF DEVIATION. Among the 137 studies that reported the prevalence of

strabismus in Down syndrome, 111 distinguished the prevalence of esotropia and exotropia, and among these 111 studies, 31 reported the number of the (relatively rare) cases of vertical deviations. Based on these 31 studies with a total of 3,991 subjects (Supplementary Table 1), we calculated a prevalence of 1.0% for vertical strabismus in Down syndrome (95% CI = 0.4-1.8%). Globally, this amounts to 18,444 Down syndrome cases with vertical deviation (Fig. 4C).

ESOTROPIA/EXOTROPIA RATIO. We compiled the geographic distribution of the prevalence of esotropia vs. exotropia, as indicated in 111 studies that reported these data (Fig. 2B). It is apparent in the world map that the esotropia/exotropia ratio is higher in Europe and North America than in the Middle East, Africa, Latin America, and most of Asia. We therefore analyzed the esotropia/exotropia ratio separately for Caucasians vs. non-Caucasians (Fig. 5A-C). The esotropia/exotropia ratio in Caucasians (including Middle East) was 9.981 (95% CI = 7.960-12.514), while in Non-Caucasians it was 3.206 (95% CI = 2.421-4.246). We estimated the number of people with Down syndrome who have esotropia or exotropia, assuming for these estimates a similar Down syndrome prevalence in different ethnicities.[167-170] The ethnicity-adjusted estimated numbers for Down syndrome people with esotropia are 346,000 of European ancestry (including Middle East), and 1.077 million non-Caucasians, for a total of 1.423 million esotropes. The numbers for Down syndrome people with exotropia are 34,700 for European ancestry (including Middle East), and 336,000 for non-Caucasians, for a total of 370,700 exotropes.

TRENDS. There were no significant longitudinal trends in strabismus prevalence in Caucasians or in the Middle East (p=0.371, and 0.699, respectively, Supplemental

Figure 2A-C). The strabismus prevalence appears to be stable over generations. However, the ET/XT ratio showed a significant decrease over time in Europeans ($p<0.001$), but there was no such trend in North America or in the Middle East ($p=0.339$, $p=0.442$, respectively, Supplemental Fig. 4A-C).

Discussion

Our systematic review and meta-analysis provide a resolution to the conflicting reports and diverse ranges of strabismus prevalence in Down syndrome reported previously (Table 1).[5-9,13-17,19,21-24,27-28,32-33,36,43,51,59,64,67,72,76,88,99-101,104,107,121,123,125,131-132,134-136,140,156,171-174] We can now estimate the global prevalence of such strabismus, take into account Eurocentric biases, define ethnic differences in the esotropia/exotropia ratio, resolve the age-dependence of strabismus prevalence, and answer questions about possible gender differences. It is currently controversial whether strabismus in Down syndrome associates with an increased degree of intellectual disability.[21,29,45,82,138,175-176] We confirm that the onset of strabismus in Down syndrome typically occurs later than in the normal population. The second half of our Discussion reviews previous and current thinking about the still mysterious etiology of strabismus in Down syndrome, and concludes that ethnic differences in the esotropia/exotropia ratio help to better understand what causes strabismus in Down syndrome.

GLOBAL PREVALENCE and NUMERICAL ESTIMATES. Our analysis established that the global prevalence of strabismus in Down syndrome is 29-39%, depending on ethnicity. When adjusted for ethnic differences, the global prevalence of strabismus in Down syndrome is 30.2% – allowing to estimate the number of Down syndrome people with strabismus at 1.81 million of the presumed 6 million people with Down syndrome.[165] The large majority of studies examining and reporting the prevalence of strabismus is based on surveys in normal schools.[177] But many children with developmental disabilities such as Down syndrome or cerebral palsy, to name just

two of the most frequent syndromes, do not attend normal schools,[9,40,42,147,154] and therefore would be excluded in most population-based studies of strabismus. Since children with Down syndrome or with cerebral palsy[178] have a much larger strabismus prevalence (30-40% – about 15-20-fold higher than in the normal population at 2%),[179] a substantial number of children with strabismus are missed in the “normal school” based studies, resulting in an undercount.

AGE AT ONSET. Previous Down syndrome studies reported that the youngest ages (0-3 years) had the lowest strabismus prevalence, while the prevalence increased with age.[4-5,10-20,31,145] The onset of strabismus (esotropia) in Down syndrome was estimated to peak at about 4.5 years of age.[5,15-16,19-20] The strabismus usually is the acquired type, not congenital, as is most common for esotropia in infants without Down syndrome.[180] This is consistent with our analysis of studies showing that the strabismus prevalence in Down syndrome at 0-3 years of age is much lower (15.6%) than the prevalence at 15 years and older (53.2%) (Figs. 3C,D, 4A). These data refute the earlier notion that the strabismus in Down syndrome spontaneously resolves in two thirds of cases.[40,65-66,100,181-183]

AMBLYOPIA. Opinions about the prevalence of amblyopia in Down syndrome are divided. The majority of studies reported that amblyopia was rare (0-5%)[5,15,23-25,28-31,144] or “uncommon” (8-14.3%),[7,21-22,26,96,100,114,160] while a smaller number of authors found a relatively large prevalence of amblyopia (16.9-36.4%)[10,12-13,27,38,109,174,184] and one study reported 54.5%.[134] However, only a relatively small fraction of the amblyopia cases associated with strabismus, meaning that the majority of amblyopia cases in Down syndrome was not caused by strabismus,[17,25-27,109,113,127,160] but some appear to

be caused by anisometropia[25,113] which is more frequent in older children with Down syndrome.[11,21,80,174] The overwhelming consensus is that, probably due to the late onset of strabismus, binocular vision is often preserved in Down syndrome.[5,15,23-31]

GENDER. There were slightly more males than females in our cohorts (sex ratio of 1.21:1), consistent with previous reports.[55-56,166] The bias towards males presumably is because of genetic mechanisms (joint segregation of chromosomes 21 and Y).[166] Similar to a previous analysis of gender in strabismus within the normal population,[185] we found no gender difference in the prevalence of strabismus in Down syndrome. There are slightly more males than females with strabismus in Down syndrome, but only because there are overall slightly more males than females with Down syndrome.

ET/XT RATIO. Ethnic differences in the esotropia/exotropia ratio were noted by several investigators.[14,17,33-39] Caucasians with Down syndrome have a further increased bias towards esotropia, with exotropia being rare, while ethnicities that normally have more exotropia than esotropia also have a bias towards esotropia when Down syndrome is present, but the esotropia/exotropia ratio is much lower (3.21) than in Caucasians with Down syndrome (9.98). The likely explanation for these ethnic differences is the difference in the orbital anatomy where the orbital width is already narrow in Caucasians, but becomes even more narrow in Down syndrome as discussed in more detail below (“Orbital Anatomy”).

ETIOLOGY OF STRABISMUS. Authors noted that strabismus in Down syndrome differs substantially from that in children without the syndrome,[19,49-51] but the reason(s) have remained enigmatic. While some authors state that the etiology of strabismus in

Down syndrome is unknown,[19,21,51,151] several possibilities have been discussed.[5,14,19,21,37,40-42,44-45,47-49,65,173,176,186] We will review them in a historical (chronologic) sequence and discuss their merits.

Orbital Anatomy. The inclination of the orbit is abnormal and the width of the orbit is much more narrow in Down syndrome.[42,99,176,187-189] Indeed, the interpupillary distance (IPD) as a measure of the orbital width is reduced in Down syndrome, by about 5-10 mm in Caucasians when compared to age-matched children or adults without Down syndrome,[3-4,21,40-42,48,64,99,146,187,190-193] and by 1-3 mm in Asians and West Africans.[156,193] For geometric-mechanistic reasons, first described in the late 19th century, optimal extraocular muscle function and binocular vision require an orbital anatomy that is within certain normal limits. When the eyes are too narrow set, or too wide set, as in Down syndrome for the narrow extreme and craniosynostosis for the wide extreme,[5,21,41,124,193-195] then esotropia or exotropia are much more likely, because the medial or lateral rectus muscles operate in a suboptimal frame.[21,41,196-205] The ethnic differences in the ET/XT ratio in Down syndrome are consistent with the notion that orbital anatomy and especially short orbital width and a narrow interpupillary distance are a major contributing factor in the etiology of the strabismus in Down syndrome.

Muscle hypotonia. Hypotonia of skeletal muscles in Down syndrome is well known.[22,44,51,55-56,95-96,170] Whether this applies to the extraocular muscles is unclear.[175] The “excessive power of the medial rectus muscles” was noted,[40] which contradicts the idea of hypotonia causing strabismus in Down syndrome.

Lens opacities/ cataract. The prevalence of cataracts is increased in Down

syndrome, especially in older individuals.[6,10,13,18-19,21,24,29, 38,43,55,57,69,71-72,82,103,105,127,142,148] Some authors proposed that lens opacities are associated with, and may be a cause of, strabismus in Down syndrome.[40,42,65,71] However, cataracts typically develop in older children, while congenital cataracts are relatively rare in Down syndrome.[4,7-8,10,17,23,27,30-33,40,64,66,68,83-84,88,90,92,99,109,114,131,135,140,145,147,150,172,186] Thus, there is a mismatch between the onset of significant lens opacities and the peak onset of strabismus in Down syndrome, indicating a minor, if any role for cataracts in the etiology of strabismus in Down syndrome.

Refractive errors. Refractive errors are the most common ocular defects in Down syndrome. Early studies implicated them as a potential cause of strabismus.[37,40,42-43,47,65-66] Most studies report more hyperopia than myopia in Down syndrome,[4-6,8,11,13-14,16-17,27-28,31-32,34-35,39,42-43,57,59-61,64,67,69,77-78,84,86,88,90-91,114,121,127,129,133-135,138,140,143,146,148-149,151,153-154,157,160,172,184,186] but about one quarter of the studies (26.4%) report more myopia than hyperopia.[15,18,21,23,26,33,63,65,72,81-82,94,105,113,119,136,141,150] Some authors stated that in Down syndrome, hyperopia is more common in Caucasians, and myopia is more common in Asians.[8,19,37,39] However, in “our” cohorts, hyperopia was about three times more frequent than myopia, in both Caucasians and Asians – more hyperopia was reported in most Asian studies,[14,17-18,32,35,135,138,140,143,146,148-149,151,153] while more myopia was reported in fewer Asian studies.[18,136-137,141,150] In normal children with refractive errors, the hyperopia can resolve over time (emmetropization), but such emmetropization does not occur in children with Down syndrome. This has been called a failure of emmetropization and has been implicated as a possible cause of strabismus in Down syndrome.[11,16,19,37,43,45,47,49,140,206] However, in contrast to normal children,[206]

there does not seem to be any convincing association between either hyperopia or myopia and development of strabismus in Down syndrome.[11,14,45,49,51,86,105,208]

Astigmatism is one of the most frequent ocular findings in Down syndrome.[7-8,10-11,14,16,35-37,43,45,63,87,104,127,144,174,208-209] Similar to the failure of emmetropization, astigmatism does not decrease with age in Down syndrome.[5,11,38-39,174] However, astigmatism does not appear to be associated with strabismus in Down syndrome.[5,11,49,87,134]

Accommodation weakness. Studies noted that the esotropia in Down syndrome often has an accommodative component.[21-22,24-25,40,42,67,96] Children with Down syndrome fail to develop an adequate accommodative convergence mechanism – an abnormality of accommodation that was subsequently described in more detail.[5,7,11,15-16,19,37-39,43,48,115,138,141,151,174,206,208-215] The possibility of this deficit being due to mechanics of a thinner cornea and lens and reduced lens power has been discussed.[16,174,209-210] Other possibilities include sensory pathway deficits,[216] peripheral motor abnormalities (ciliary muscle), or central abnormalities (neuronal control of the ciliary muscle).[59,208-210,213,217] The ciliary muscle appears normal in Down syndrome.[16] Potential defective neural control of accommodation may be a manifestation of a general cholinergic deficit in Down syndrome.[218] The interplay of accommodation weakness, hyperopia, and a decreased interpupillary distance in Down syndrome may precipitate strabismus.[219] Use of bifocals improves accommodation accuracy, near visual acuity, and reduces the degree of deviation in small-angle esotropic Down syndrome children.[173,214,221,222]

Visual acuity and contrast sensitivity. Several studies revealed deficits in visual acuity and contrast sensitivity in Down syndrome that developed after one year of age.[111,216,223-225] These deficits may be due to pre-retinal (optic) abnormalities, they could be cortical, a consequence of accommodation weakness, or a combination of the above factors.[16,37,111,216,223,226-227] The cornea and lens are thinner in Down syndrome, as mentioned.[16,174,208-210] Although the fovea of the retina has an abnormal thickness and layering in Down syndrome and also in animal models of Down syndrome,[46,228-229] a thicker macula does not seem to correlate with reduced visual acuity.[228] Regarding a possible cortical contribution, the visual cortex of Down syndrome children has age-related abnormalities in the neuronal architecture, with reduced dendritic arborizations and reduced neuronal densities,[16,37,230-236] as well as slightly reduced synaptic density (by 1-9% at ages 4-9 years),[234] but such reports await confirmation with modern stereological methods.[237] Recent analyses concluded that there are no profound disruptions in synaptic formation and/or pruning in Down syndrome.[238] While a lesion of inputs to visual cortex can cause strabismus,[239] it is unclear to what extent subtle cortical abnormalities in Down syndrome (lacking any acute injury) may contribute to reduced binocular vision processing and the development of strabismus. On the basis of exotropia being more frequent than esotropia in cases of brain damage, Haugen and Hovding[5] argued against a major contribution of cortical abnormalities causing strabismus in Down syndrome. Also, there is no direct evidence showing that the minor visual cortex abnormalities in Down syndrome contribute to strabismus.

Combination of sub-normal conditions. Multiple factors rather than a single factor along the sensory-motor loops (optic apparatus, retina, visual cortex, oculomotor nuclei,

extraocular muscles, orbital anatomy)[240-241] may be necessary to elicit strabismus in Down syndrome. Given the ethnic differences in the esotropia/exotropia ratio and their correlation with orbital anatomy, the orbital width appears to be a major factor.

Conclusion

A large number of people with Down syndrome have strabismus: about 1.81 million, with a lifetime prevalence of 3.19 million. There are major ethnic differences in the esotropia/exotropia (ET/XT) ratio, with Caucasians having a high ET/XT ratio (9.98), while this ratio is much lower in other ethnicities (3.21). Surprisingly, the abnormal orbital anatomy in Down syndrome is rarely considered as contributing or being a major cause of strabismus, even though an abnormal width of the orbit is a known risk factor for strabismus.[41,194-195,198,204] Ethnic differences in the ET/XT ratio support the notion that orbit differences substantially contribute to the etiology of strabismus in Down syndrome. A combination of retinal differences, cortical abnormalities, accommodation weakness, blurry vision, together with abnormally narrow orbital width produces multiple conditions of sub-normality in Down syndrome that may prevent the development of normal binocular processing.[42,242]

Acknowledgments

We thank Jenny Costa (University of Nevada, Reno, School of Medicine) for her help with retrieving sources. We also thank Michael Herron and Mitchell Strominger (University of Nevada, Reno School of Medicine), Zainab Zehra (COMSATS University, Islamabad, Pakistan), and Wei Yang (University of Nevada, Reno School of Public Health) for helpful comments.

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FIGURES

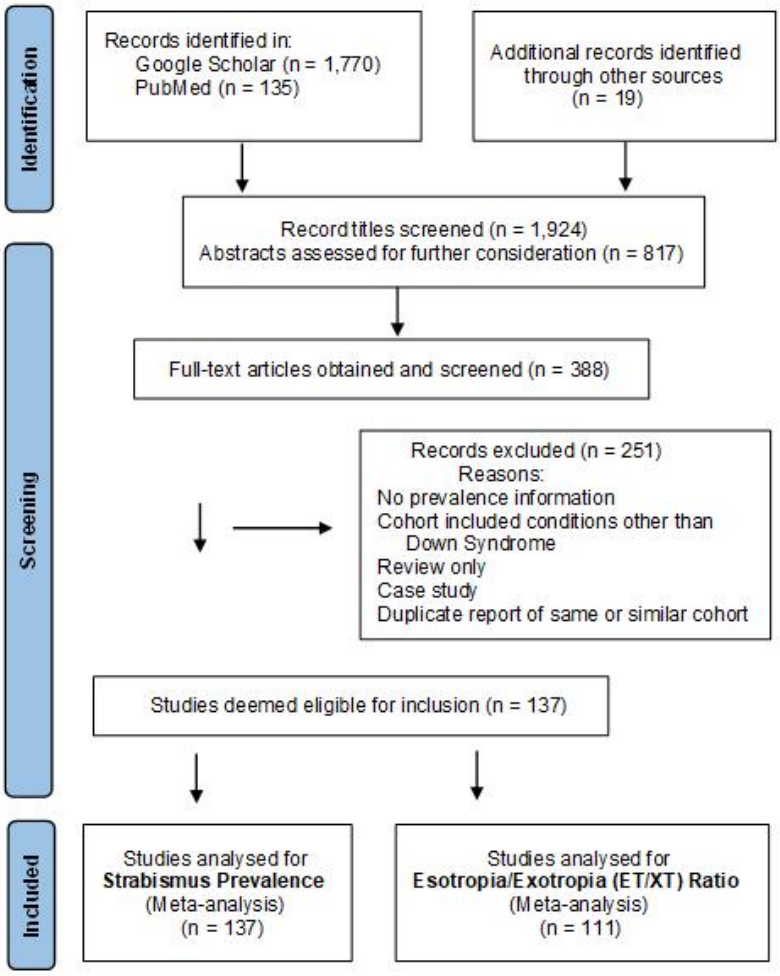


Fig. 1. Flowchart of the Literature Search.

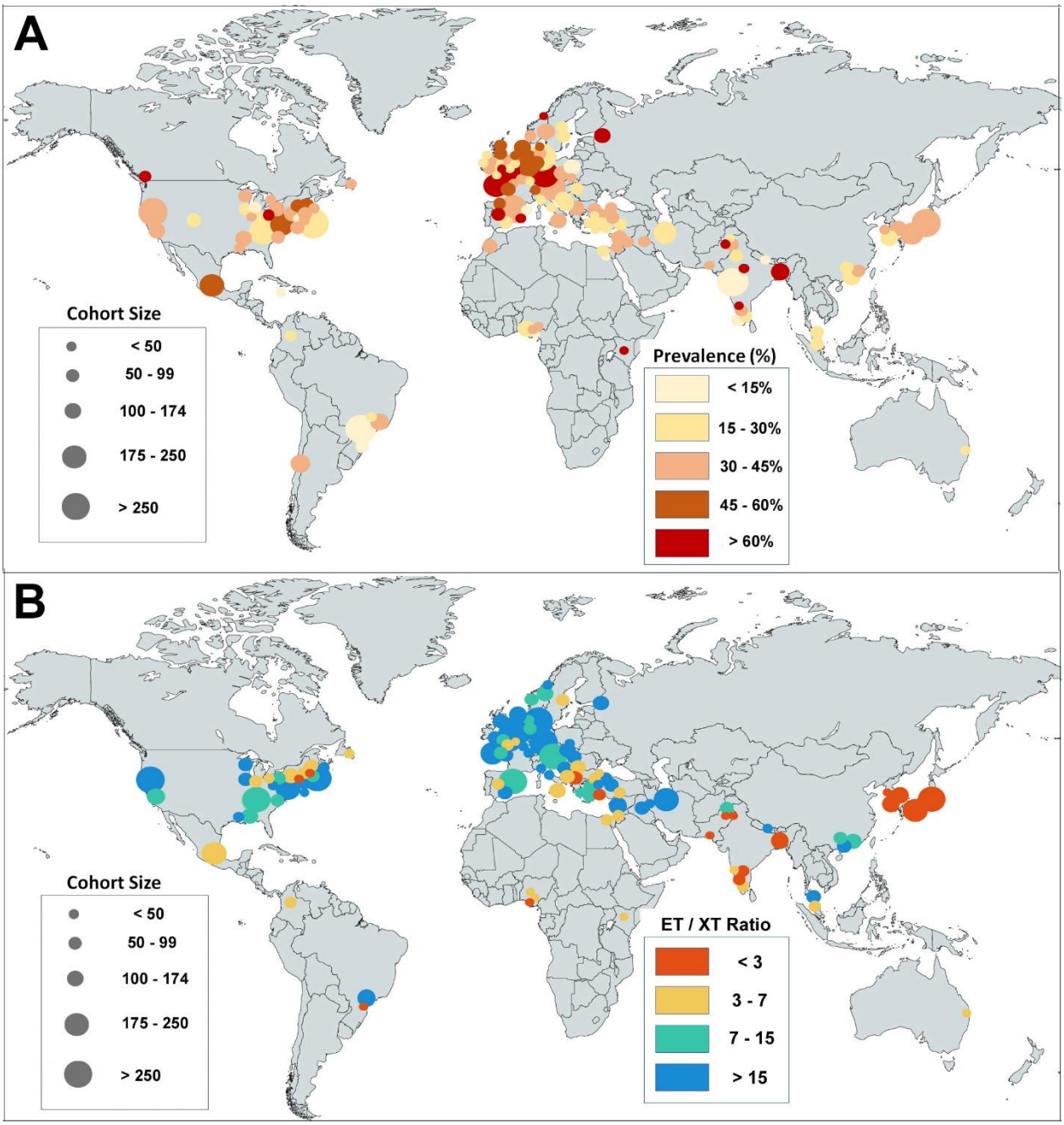


Fig. 2A,B. Distribution of studies reporting the prevalence of strabismus in Down syndrome (**A**) and distribution of studies reporting the esotropia / exotropia (ET/XT) ratio in Down Syndrome (**B**). The prevalence and ET/XT ratio are indicated in a heat map. Cohort Sizes are indicated by the size of the circles.

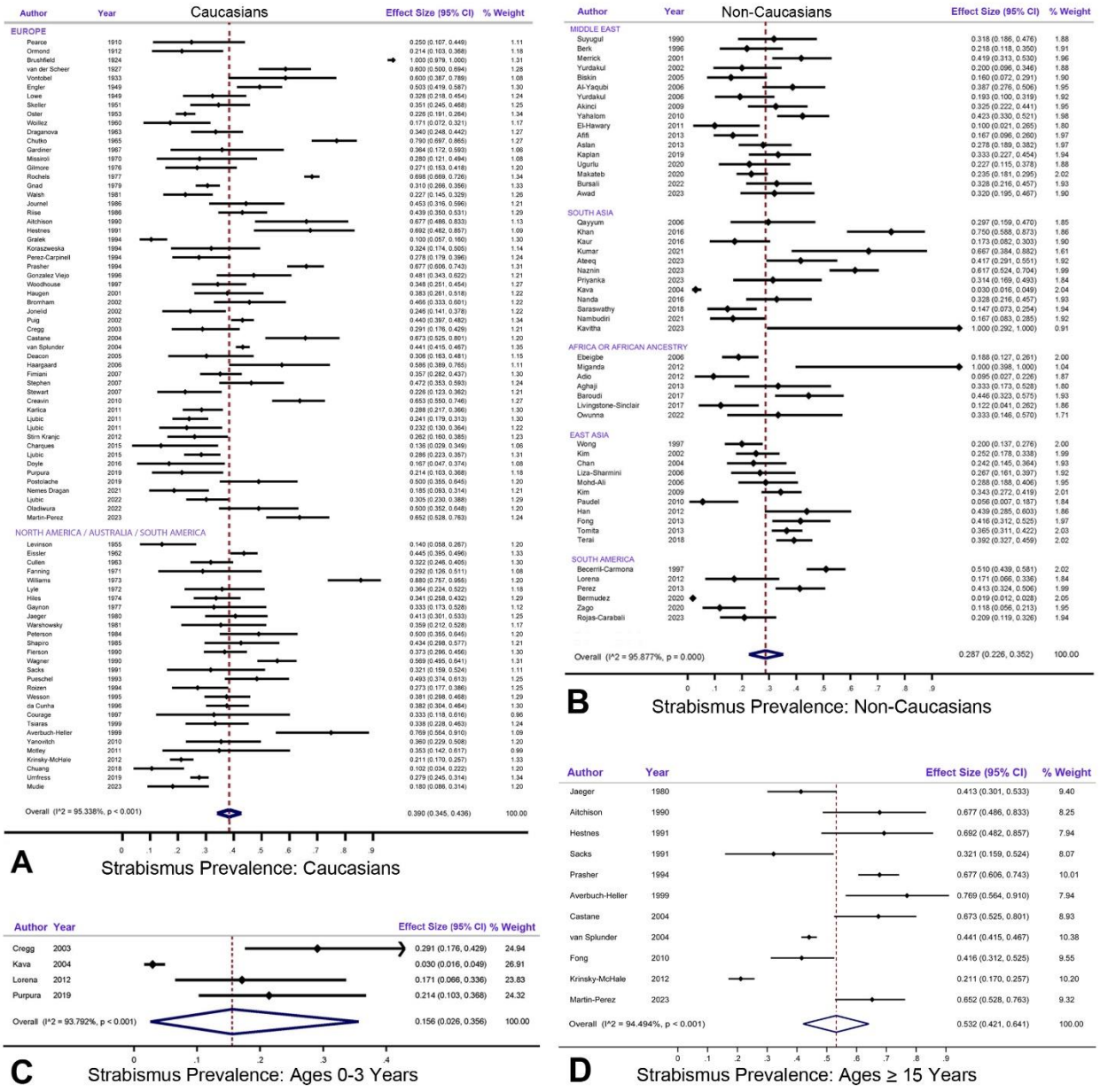


Fig. 3A-D. Forest Plots show the strabismus prevalence in Down syndrome. CI, confidence interval; $I^{\wedge 2}$ indicates the level of heterogeneity. **A**. In Caucasians. **B**. In Non-Caucasians (Middle East, South Asia, Africa, East Asia, South America). **C**. Ages 0-3 years. **D**. Ages 15 years and older.

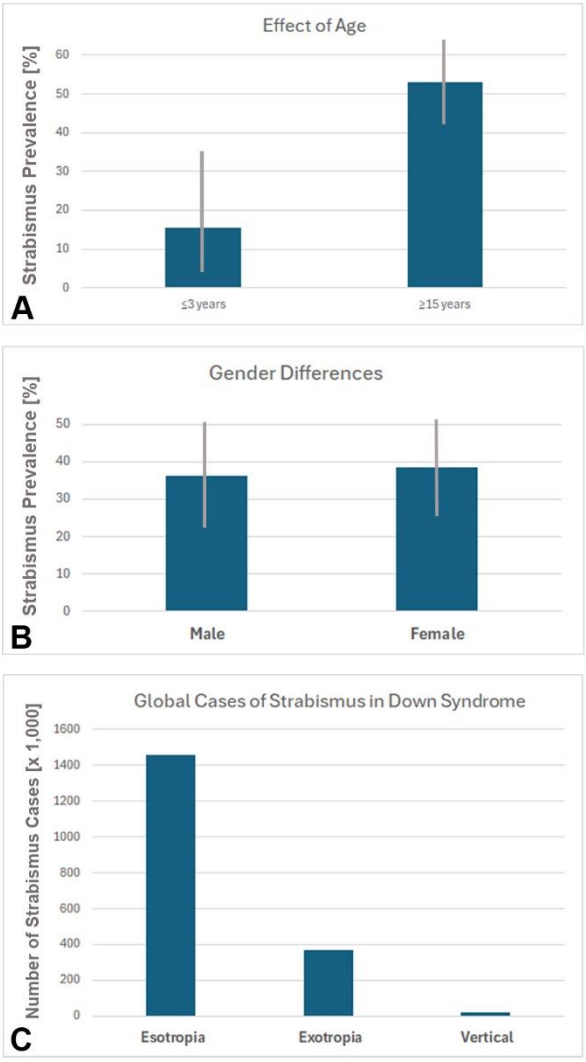


Fig. 4A-C. Graphs showing significant differences in strabismus prevalence by age **(A)** <3 years and 10 years and older, no difference in prevalence by gender **(B),** and the estimated number of people with Down syndrome having esotropia, exotropia and vertical deviations **(C).** Error bars in A,B = 95% confidence intervals.

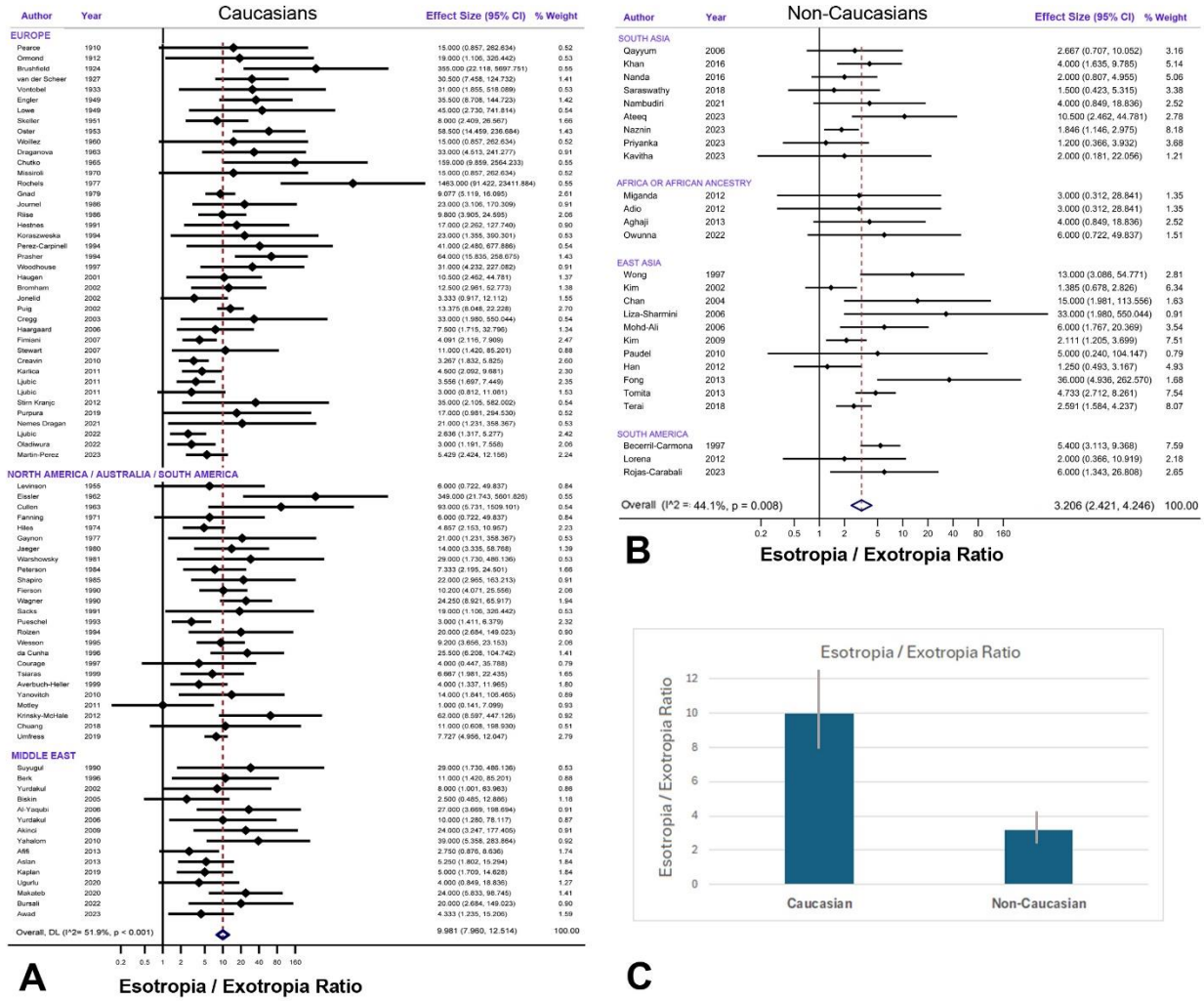


Fig. 5A-C. Forest plots of the Esotropia/Exotropia Ratio in Down syndrome for Caucasians and populations from the Middle East **(A),** and Asians, Africans and Hispanics **(B).** CI, confidence interval; $I^{\wedge 2}$ indicates the level of heterogeneity. Bar graph shows the esotropia/exotropia ratio in Caucasians vs Non-Caucasians with Down syndrome **(C),** with error bars indicating the 95% confidence intervals**.**

TABLES

Table 1. Forty different ranges of strabismus prevalence in Down syndrome according to previous authors.

First Author	Ref. #	Year	Prevalence Range	# of Studies Considered	# of Subjects in all Cohorts
Woillez	59	1960	7.7% to 45%	5	202+
Falls	171	1970	12% to 23%	3	770
Missiroli	64	1970	21.4% to 50%	6	745+
Lyle	99	1972	12% to 60%	4	121+
Hiles	100	1974	12% to 50%	4	603+
Gaynon	101	1977	32% to 44%	4	564
Gnad	67	1979	33% to 79%	5	1,459
Jaeger	21	1980	30% to 50%	5	787
Shapiro	104	1985	21% to 44%	7	900
Catalano	22	1990	23% to 44%	10	1,004
Wagner	107	1990	21% to 44%	7	972
Hestnes	72	1991	23% to 79%	10	2,166
Prasher	76	1994	33% to 69%	6	818
Roizen	23	1994	27% to 57%	5	266
Berk	121	1996	13% to 44%	7	839
Davis	24	1996	23% to 44%	2	466
Wong	135	1997	12% to 57	7	507
Haugen	5	2001	19% to 70%	15	2,352
Kim	32	2002	13% to 57%	9	1,296
Yurdakul	13	2002	20% to 38%	5	373
Chan	136	2004	20% to 38%	4	481
Ji	43	2006	9% to 69%	10	762
Yurdakul	27	2006	21% to 44%	11	1,314
Fimiani	28	2007	22% to 57%	7	787
Molina	172	2008	19% to 42%	7	564
Creavin	6	2009	3% to 60%	20	2,286
Kim	14	2009	20% to 57%	6	704
Paudel	140	2010	12% to 44%	11	1,125
Yahalom	123	2010	20% to 50%	6	343
Karlica	33	2011	20% to 57%	5	600
Morton	7	2011	24% to 46%	13	1,489
Adio	156	2012	5.6% to 27%	7	597
Afifi	8	2013	6% to 88%	31	3,507
Aslan	125	2013	12% to 46%	6	659
Perez	131	2013	20% to 60%	5	553
Miyazaki	15	2014	20% to 60%	6	585
Ljubic	88	2015	20% to 57%	9	1,172
Watt	16	2015	19% to 34%	3	269
Nanda	17	2016	20% to 57%	6	651
de Weger	173	2019	15% to 47%	5	379
Bermudez	132	2020	1.9% to 38%	6	1,757
Harrison	51	2020	19% to 42%	5	526
Makateb	9	2020	5.6% to 65%	16	2,312
Sousa	36	2020	30% to 45%	4	713
Mathan	174	2022	18% to 57%	4	601
Rojas-Carabali	134	2023	9.5% to 38%	7	653

Sun	19	2023	9.5% to 57%	7	1,249
current review		2025	1.9% to 100%	137	16,781

The most frequent ranges are 20-57% (4 times), 21-44% (3 times), 19-42% (2 times), 20-38% (2 times).
+, additional reviews were cited, or not-verified sources were quoted

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Prevalence of strabismus, esotropia (ET), exotropia (XT), vertical deviation (Vert.) and all strabismus (All Strab.) in cohort studies of Down syndrome. Ref., Reference. The Table is organized by region/ethnicity as well as chronological within those regions. Explanations: +, a few subjects in the cohort exceeded the range; blank, no information was given. N=142 studies; shaded: duplicate reports of the same cohort.

First Author	Ref. #	Year	Region	Age (years)	Cohort size	ET %	XT %	ET/XT Ratio	Vert. %	All Strab.
EUROPE										
Pearce	1	1910	Redhill, S London, UK	5-43	28	25	0	15*		25%
Ormond	2	1912	S London, UK	5-43	42	21.4	0	19*		21.4%
Brushfield	3	1924	London, UK	2-14	177	100	0	355*		100%
van der Scheer	55	1927	Haarlem, Netherlands	2-36	105	58	2	29		60%
Vontobel	4	1933	Switzerland	1-40	25	60	0	31*		60%
Engler	56	1949	London, UK	2-54	145	49	1.4	35		50.4%
Lowe	40	1949	London, UK	5-60	67	32.8	0	45*		32.8%
Skeller	57	1951	Denmark	<58	77	31.2	3.9	8.0	1.3	35%
Oster	58	1953	Denmark	0-75	526	22.2	0.4	58.5	0	22.6%
Woillez	59	1960	Lille, France	4-17	41	17	0	15*		17%
Draganova	60	1963	Czechia	0-36	100	33	1	33		34%
Siebeck	61	1964	UK	children	79	49.4	1.3	39		50.6%
Chutko	62	1965	St. Petersburg, Russia	<18	100	79	0	159*		79%
Gardiner	63	1967	London, UK	5-16	22					36.4%
Missiroli	64	1970	Rome, Italy	12-42	25	28	0	15*		28%
Gilmore	65	1976	Dublin, Ireland	6-57	48					27.1%
Rochels	66	1977	Mainz, Germany	1-23	1047	69.8	0	1463*		69.8%
Gnad	67	1979	Austria	0-14	420	28	3	9.33		31%
Walsh	68	1981	Stockholm, Sweden	5-60	88					23%
Journel	69	1986	Rennes, France	0-13+	53	43.4	1.9	22.84		45.3%
Riise	70	1986	Lillehammer, Norway	0-66	123	40	4	10.00		44%
Aitchison	71	1990	Bristol, UK	21-65	31					69.2%
Hestnes	72	1991	Trondheim, Norway	20-60	26	65.4	3.8	17.21		69.2%
Gralek	73	1994	Lodz, Poland	0-18	150					10%
Koraszweska	74	1994	Katowice, Poland	0.5-14	34	32.4	0	23*	0	32.4%
Perez-Carpinell	75	1994	Valencia, Spain	7-22	72	28	0	41*		28%
Prasher	76	1994	Birmingham, UK	16-76	192	66.7	1.04	64		67.7%
Gonzalez Viejo	77	1996	Zaragoza, Spain	4-8	54					48.3%
Woodhouse	11	1997	Wales, UK	0-12	92	34	1	34		35%
Haugen	5	2001	Bergen, Norway	2-12	60	35	3.3	10.61		38.3%
Bromham	78	2002	Wales, UK	1-9	58	43.1	3.4	12.68		46.5%
Jonelid	79	2002	Uppsala, Sweden	0.5-21	57	17.5	5.3	3.33	1.8	25%
Puig	80	2002	Barcelona, Spain	0-18	546	39.2	2.9	13.7	1.3	44%

Cregg	49	2003	Wales, UK	2-3	55	29.1	0	33*		29.1%
Castane	81	2004	Barcelona, Spain	40-62	49					66.7%
van Splunder	82	2004	Netherlands	20-89	1,441					44.1%
Deacon	50	2005	Wales, UK	0.5-17	36					30.5%
Haargaard	83	2006	Denmark (natl)**	0-17	29	51.7	6.9	7.5	0	58.6%
Fimiani	28	2007	Naples, Italy	0-18	157	28.7	7	4.1		35.7%
Stephen	84	2007	Aberdeen, UK	0-5.5	72					47.2%
Stewart	44	2007	Wales, UK	1-13	53	20.8	1.9	10.95		22.7%
Creavin	85	2010	Bristol, UK	0-16	98	50	15.3	3.3		65%
Karlica	33	2011	Split, Croatia	0-18	153	23.5	5.2	4.5		28.7%
Ljubic	86	2011	Macedonia	1-34	170	18.8	5.3	3.55	2.4	24.1%
Ljubic	87	2011	Macedonia	2-28	56	16.1	5.4	3.0	1.8	23.2%
Stirn Kranjc	34	2012	Slovenia	0-13	65	26.2	0	35*		26.2%
Charques	47	2015	Barcelona, Spain	8-40	22					13.6%
Ljubic	88	2015	Macedonia, Croatia	2-34	185					28.6%
Doyle	48	2016	Ulster, N Ireland	6-16	24			(3.0?)		16.7%
Postolache	89	2019	Brussels, Belgium	6-14	50					50.0%
Purpura	90	2019	Pisa, Florence, Italy	0-3	42	19.0	0	17*	2.4	21.4%
Nemes Dragan	91	2021	Oradea, Romania	9 (mean)	54	18.5	0	21*		18.5%
Ljubic	92	2022	Croatia, North Macedonia	2-34	141	20.6	7.8	2.6	2.1	30.5%
Oladiwura	93	2022	London, UK	0-26	48	37.5	12.5	3.0	0	50.0%
Martin-Perez	94	2023	Madrid, Spain	17-35	69	55	9.7	5.7		64.7%
NORTH AMERICA, AUSTRALIA (mostly Caucasians)										
Levinson	95	1955	Chicago, USA	1-17	50	12	2	6.0		14%
Eissler	96	1962	San Francisco, USA	1-59	391	44.4	0	349*		44.4%
Cullen	97	1963	Maryland, USA	2-53	143	32.2	0	93*		32.2%
Fanning	42	1971	Brisbane, Australia	6-18	24	25	4.2	5.95		29.2%
Williams	98	1973	Vancouver, Canada	10-25	50					88%
Lyle	99	1972	Ontario, Canada	5-29	44					36%
Hiles	100	1974	Pittsburgh, USA	children	123	28	6	4.67		34%
Gaynon	101	1977	Hammond, Louisiana	10-50	30	33.3	0	21*		33.3%
Jaeger	21	1980	Philadelphia, USA	15-64	75	37.3	2.7	14.0	1.3	41.3%
Warshowsky	102	1981	New York, USA	2-8	39	35.9	0	29*		35.9%
Petersen	103	1984	Boston, USA	children	50	44	6	7.33		50%
Shapiro	104	1985	Wisconsin, USA	7-36	53	41.5	1.9	22.0		43.4%
Caputo	105	1989	New Jersey, USA	1-26	187	51.9	2.1	24.71	3.2	57.2%
Fierson	106	1990	Los Angeles, USA	0-19	150	34	3	11.33		37%
Wagner	107	1990	New Jersey, USA	0-24	188	51.6	2.1	24.57	3.2	56.9%
Sacks	108	1991	Cincinnati, USA	21-64	28	32.1	0	19*		32.1%
Pueschel	109	1993	Rhode Island, USA	5-18	73	37	12.3	3.01		49.3%
Roizen	23	1994	Chicago, USA	0-19	77	26	1	26		27%
Wesson	110	1995	Birmingham, USA	mean 4.5	134	34	4	8.50		38%

Courage	111	1997	Newfoundland, Canada	0-14	15	26.7	6.7	4.0		33.3%
Averbuch-Heller	112	1999	Cleveland, Ohio, USA	31-51	26	61.5	15.4	4.0		76.9%
Tsiaras	113	1999	Rhode Island, USA	5-19	68	29.8	4.5	6.62		34.3%
Yanovitch	114	2010	Durham, USA ¾ white, ¼ black	3-10	50	28	2	14		36%
Motley	115	2011	Cincinnati, USA (white)	0-35	17	11.8	11.8	1	11.8	35%
Krinsky-McHale	29	2012	New York, USA	30-80+	355	17.4	0.4	39.5		21.1%
Duckman	116	2014	Kew Gardens, New York	2-5	42	26.2	16.7	1.57	0	42.9%
Chuang	117	2018	New Haven, USA	1-8	49	10.2	0	11*	0	10.2%
Umfress	31	2019	Tennessee, USA	<18	689	24.7	3.2	7.72		27.9%
Mudie	118	2023	Colorado, USA	1-14	50					18%
MIDDLE EAST										
Suyugul	119	1990	Istanbul, Turkey	0.3-16	44	31.8	0	29*		31.8%
Suyugul	120	1992	Istanbul, Turkey	0.3-16	44					31.8%
Berk	121	1996	Izmir, Turkey	0-25	55	20	1.8	11.1		21.8%
Merrick	122	2001	Tel Aviv, Jerusalem, Israel	5-18	86					41.3%
Yurdakul	13	2002	Izmir, Turkey	2-20	45	18	2	9.00	0	20%
Biskin	12	2005	Antalya, Turkey	0-18	50	10	4	2.5	2	16%
Al-Yaqubi	26	2006	Baghdad, Iraq	6-18	75	36	1.3	27.7	1.3	38.7%
Yurdakul	27	2006	Izmir, Turkey	1-31	57	17.5	1.7	10.0		19.3%
Akinci	45	2009	Ankara, Turkey	1-17	77	31.2	1.3	24.0		32.5%
Yahalom	123	2010	Jerusalem, Israel	1-25	111	35.1	0.9	39.0		42%
El-Hawary	124	2011	Cairo, Egypt	2-13	30	10				10%
Afifi	8	2013	Cairo, Egypt	0-10	90	12	4	3.0		17%
Aslan	125	2013	Kahramanmaras, Turkey	4-12	90	23.3	4.4	5.30		27.7%
Kaplan	126	2019	Istanbul, Turkey	1-22	72	27.8	5.6	4.96	0	33.4%
Ugurlu	127	2020	Istanbul, Turkey	7-18	44	18.2	4.5	4.04		22.7%
Makateb	9	2020	Tehran, Iran	10-30	226	21.2	0.9	23.6	1.8	23.4%
Bursali	128	2022	Sakarya, Turkey	<18	64	31.2	1.5	20.8	0	32.7%
Awad	129	2023	Gaza	10-16	50	26	6	4.33		32%
SOUTH ASIA (NORTH)										
Qayyum	146	2006	Lahore, Pakistan	children	37	21.6	8.1	2.67		29.7%
Khan	148	2016	Lahore, Pakistan	6-14	40	60	15	2.67		75%
Kaur	147	2016	Punjab, India	3-16	52					17.3%
Kumar	150	2021	Jhansi, N. India	1-10	15					68%
Ateeq	20	2023	Lahore, Pakistan	2-18	60	35.0	3.3	10.5	3.3	41.7%
Naznin	18	2023	Dhaka, Bangladesh	1-16	120	40	21.7	1.85	0	61.6%
Priyanka	153	2023	Karachi, Pakistan	5-25	35	17.1	14.3	1.2		31.4%
SOUTH ASIA (SOUTH AND CENTRAL)										

Kava	145	2004	Mumbai, India	0-26	471***					3.0%
Nanda	17	2016	Bangalore, India	1-14	64	21.9	10.9	2.01		32.8%
Saraswathy	149	2018	Kerala, India	5-17	68	8.8	5.9	1.5		14.7%
Nambudiri	151	2021	Kerala, India	2-18	60	13.3	3.3	4.03		16.6%
Kavitha	152	2023	Karnataka, India	1-15	3	66.7	33.3	3.0		100%
AFRICA OR AFRICAN ANCESTRY										
Ebeigbe	154	2006	Benin City, Nigeria	6-19	144	“Majority ET”				18.8%
Miganda	155	2012	Samburu County, Kenya	4-15	4	75	25	3		100%
Adio	156	2012	Port Harcourt, Nigeria	1-28	42	7.1	2.4	2.96		9.5%
Aghaji	157	2013	Enugu, Nigeria	5-15	30	26.7	6.7	3.99		33.3%
Baroudi	158	2017	Marrakesh, Morocco	children	65					44.6%
Livingstone-Sinclair	159	2017	Jamaica	1-12	41					11%
Owunna	160	2022	Imo State, Nigeria	5-25	21	28.6	4.7	6.09		33.3%
EAST ASIA										
Wong	135	1997	Hong Kong, China	0-13	140	18.6	1.4	13.3		20%
Kim	32	2002	Seoul, Korea	0-14	123	14.6	10.6	1.38	0	25%
Chan	136	2004	Hong Kong, China	2-18	66	22.7	1.5	15	0	24.2%
Liza-Sharmini	137	2006	Kelantan, Malaysia	0-17	60	26.7	0	33*		26.7%
Mohd-Ali	138	2006	Kuala Lumpur, Malaysia	1-12	73	24.7	4.1	6.02		28.7%
Kim	14	2009	Seoul, Korea	0->9	172	22.1	10.5	2.10	1.3	34.3%
Fong	139	2010	Hong Kong, China	30-56	89	40.4	1.1	36		41.5%
Paudel	140	2010	Kathmandu, Nepal	0-18	36	5.6	0	5*		5.6%
Han	141	2012	Incheon, Korea	2-36	41	23.4	19.5	1.25		43.9%
Fong	142	2013	Hong Kong, China	30-56	89	40.4	1.1	36		41.5%
Tomita	143	2013	Tokyo, Japan	1-14	304	23.3	4.9	4.73	8.2	36.5%
Tomita	144	2017	Tokyo, Japan	0-12	125	26.4	4.0	6.6	4.8	35.2%
Terai	35	2018	Shiga, Japan	0-19	222	25.7	9.9	2.60	0.5	39.2%
SOUTH AMERICA										
da Cunha	130	1995	Sao Paulo, Brazil	0-18	152	31.6	1.3	24.0	2.6	35.5%
da Cunha	10	1996	Sao Paulo, Brazil 87% were white	0-18	152	33.6	1.3	25.8	2.6	38%
Becerril-Carmona	25	1997	Mexico City, Mexico	1-40	200	40.5	7.5	5.4	3.0	51.0%
Lorena	30	2012	Sao Paulo, Brazil	0.2	35	11.4	5.7	2.00		17.1%
Perez	131	2013	Santiago, Chile	1-15	121					41.6%
Bermudez	132	2020	Parana, Brazil (Curitiba, Brazil)	0-31+	1,207					1.9%
Zago	133	2020	Blumenau, Brazil	0-25	76					11.8%
Rojas-Carabali	134	2023	Colombia, Bogota	8-16	67	17.9	3.0	6.0		21.5%

* When calculating the ET/XT ratio, a continuity correction of 0.5 was applied to studies with zero XT cases by adding 0.5 to both ET and XT to avoid division by zero.

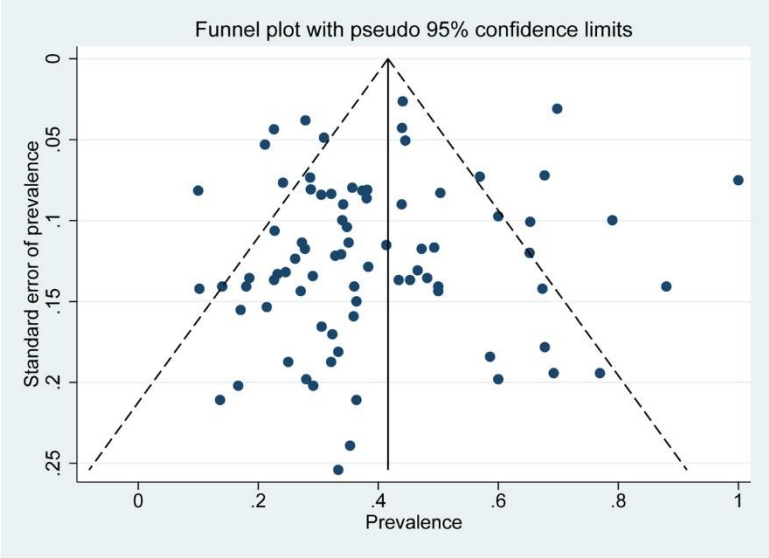
** natl, national = throughout the country

*** Excludes neonates

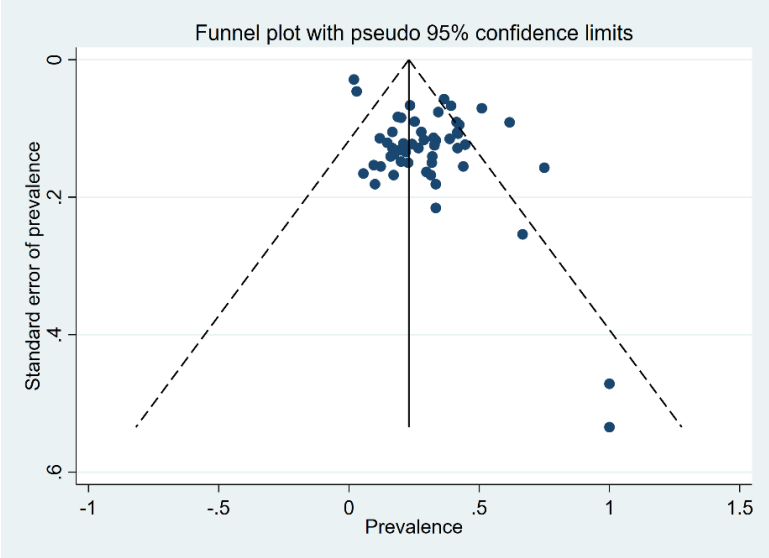
Gray-shade, studies reporting (largely) on duplicate cohorts

Ethnicity vs. Geography grouping in meta-analysis: Some studies in multiracial countries provided information about the ethnicity or the prevailing ethnicity within the cohort. For example, Duckman (2014) reported on subjects of mostly Asian and African ancestry in their cohort, and therefore, this cohort was not included in the meta-analysis as a Caucasian cohort. Likewise, one South American study (da Cunha et al., 1996) reported a large majority of European ancestry in their cohort, and this cohort was therefore included among the Caucasian (European ancestry) cohorts in the meta-analysis.

SUPPLEMENTARY FIGURES

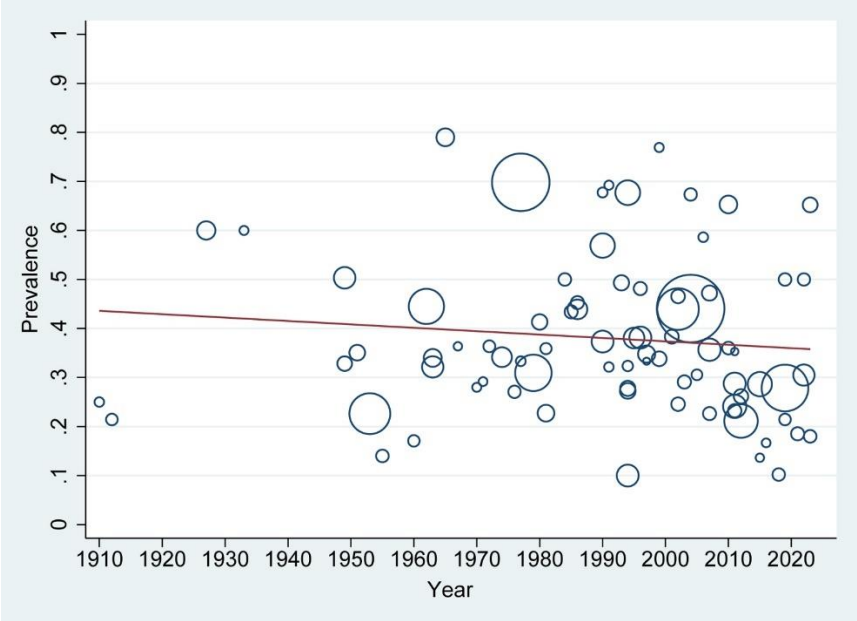


A. Strabismus Prevalence – Caucasians with Down syndrome. No Publication bias. Egger's test p=0.180

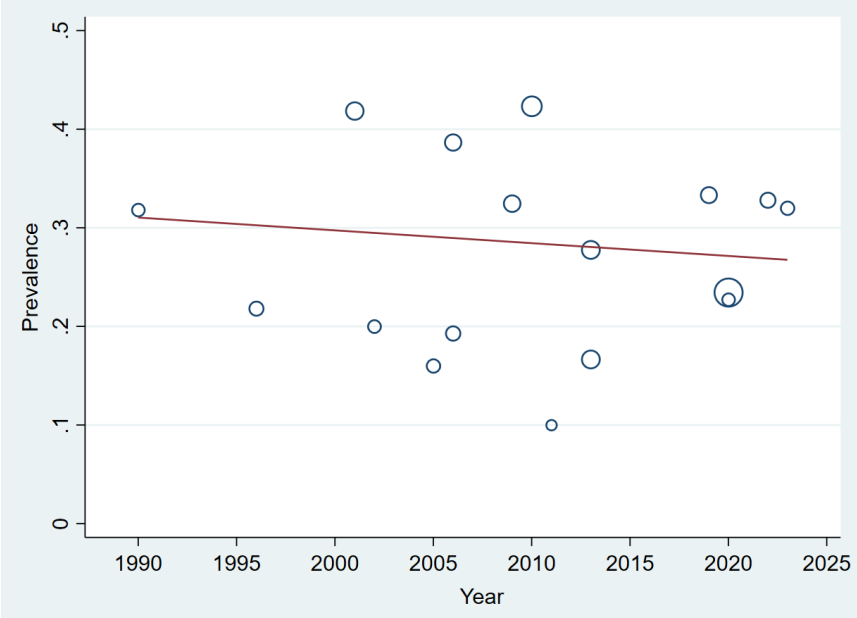


B. Strabismus Prevalence – Non-Caucasians with Down syndrome. Publication bias. Egger's test p<0.001

Supplemental Fig. 1A,B. Funnel Plots for the prevalence of strabismus in Down syndrome in Caucasians (**A**, n=84 studies) and for Non-Caucasians (**B**, n=53 studies).

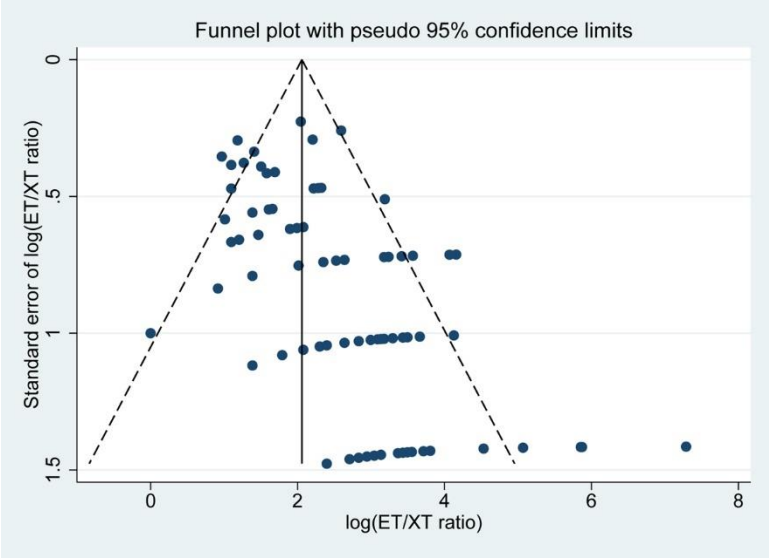


A. No Trend in Strabismus Prevalence for Caucasians with Down syndrome according to the bubble plot (p=0.371)

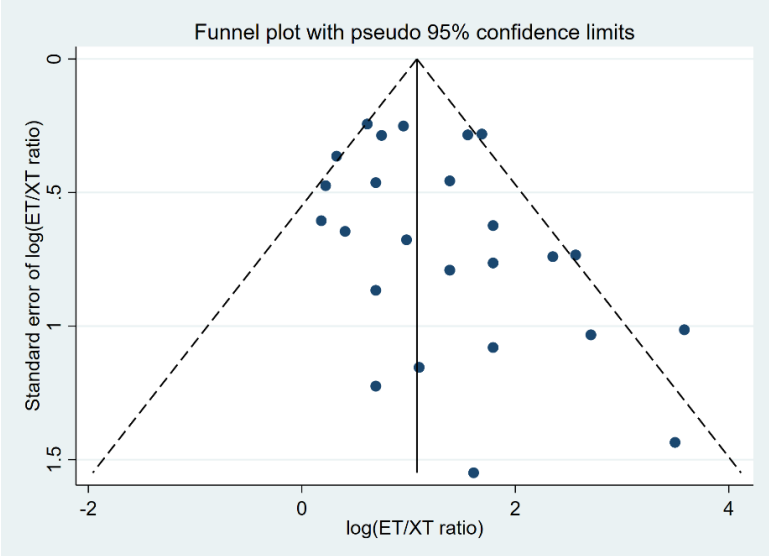


B. No Trend in Strabismus Prevalence for Down syndrome in the Middle East according to the bubble plot (p=0.699)

Supplemental Fig. 2A,B. Bubble plots showing Longitudinal Analysis for Trends in Strabismus Prevalence for people with Down syndrome in Caucasians (**A**) and in the Middle East (**B**): no generational changes. We identified two outliers in studies on Caucasians (Brushfield, 1924; Williams et al., 1973)[3,98] using Tukey's Hinges with k=1.5. These outliers were excluded from the longitudinal trend analysis.

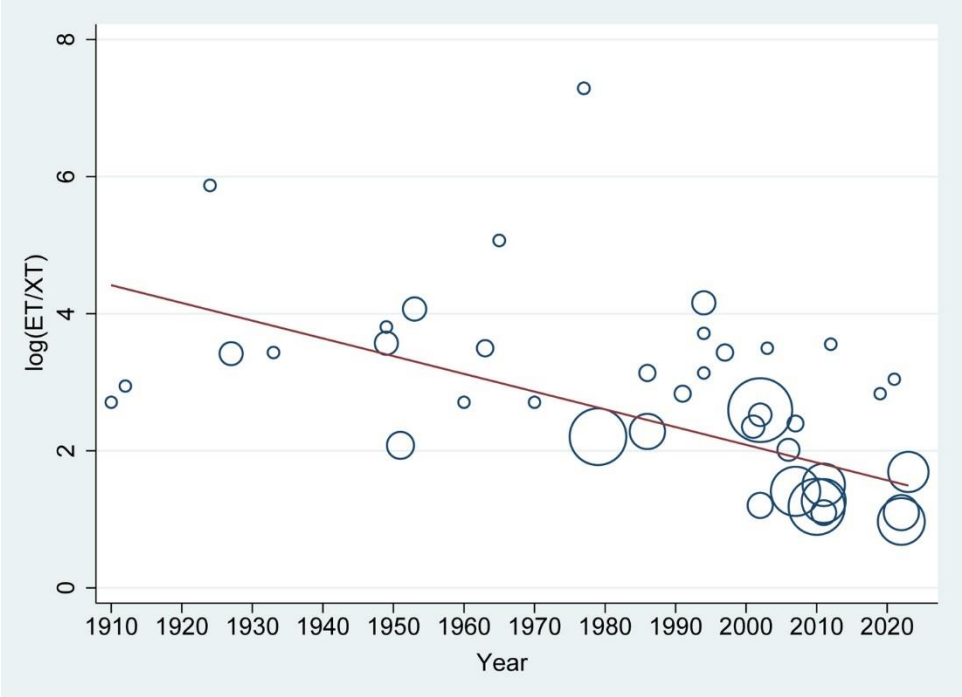


A. Funnel Plot for the Esotropia/Exotropia Ratio in Down syndrome in Europe, North America and the Middle East: Possible publication bias according to Egger's test (p<0.001)

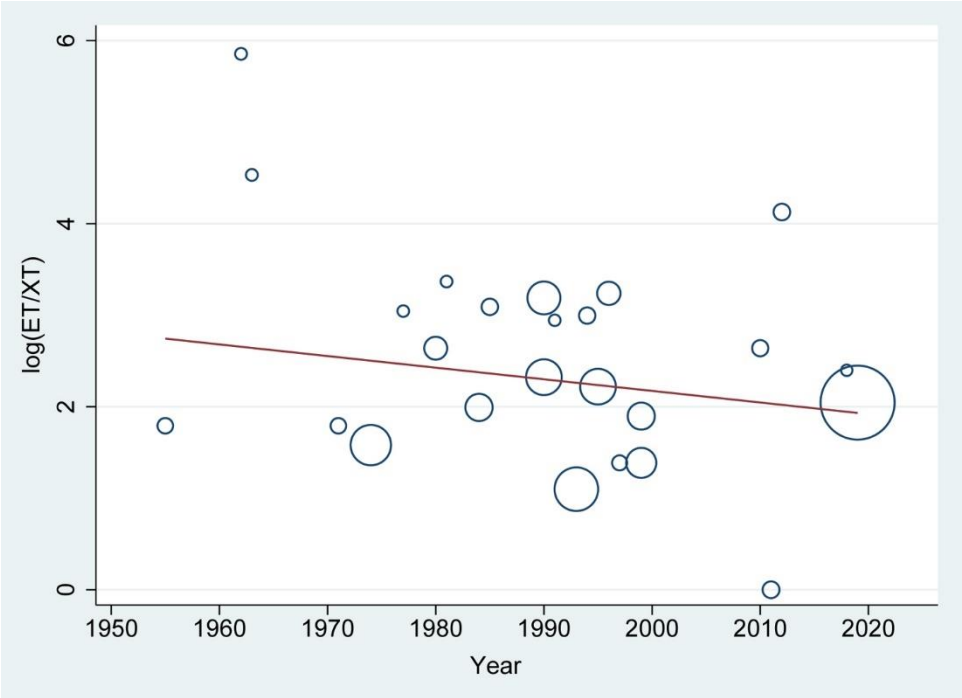


B. Funnel Plot for the Esotropia/Exotropia Ratio in Down syndrome in Non-Caucasians (Asia, Africa, South America): No publication bias according to Egger's test (p=0.075)

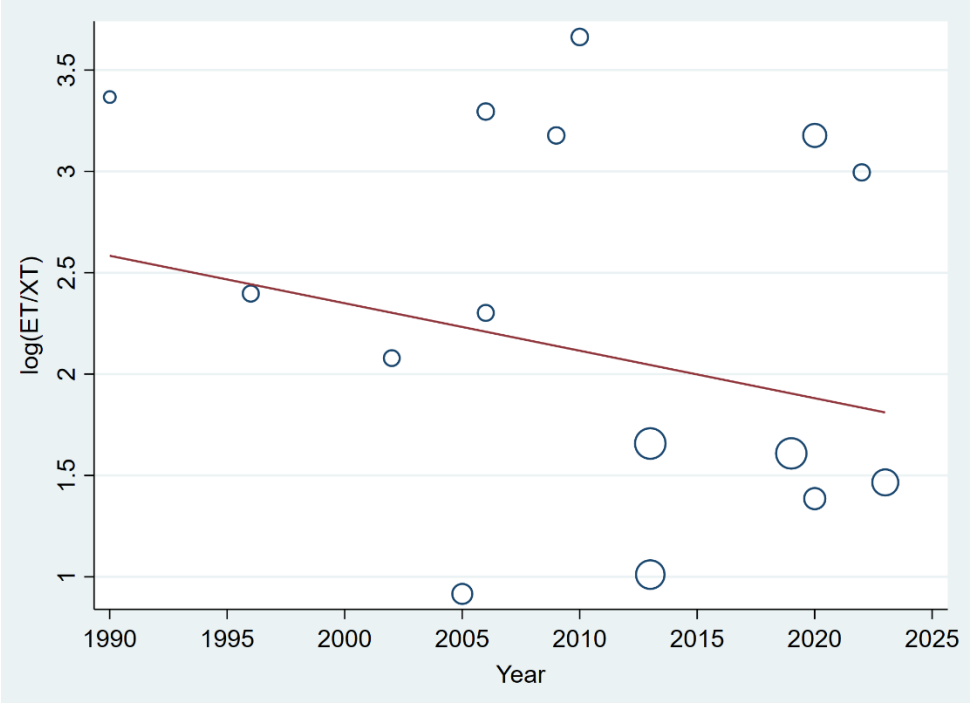
Supplemental Fig. 3A,B. Funnel Plots showing possible publication bias in the Esotropia/ Exotropia Ratio in Caucasians with Down syndrome (**A**), but not in Non-Caucasians (**B**).



A. Decreasing trend in the Esotropia/Exotropia Ratio in Down syndrome according to the bubble plot for Europe (p<0.001)



B. No significant trend in the Esotropia/Exotropia Ratio in Down syndrome according to the bubble plot for North America, Australia (p=0.339)



C. No significant trend in the Esotropia/Exotropia Ratio in Down syndrome according to the Bubble Plot for the Middle East (p=0.442)

Supplemental Fig. 4A-C. Bubble Plots showing Longitudinal Analysis for Trends in the Esotropia/Exotropia Ratio in Down syndrome: Generational changes in Europeans (**A**), but not in North America (**B**) or in the Middle East (**C**).